

## OBEZİTE VE COVID-19 İLİŞKİSİ

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### GİRİŞ

Koronavirüsler, bazı konakçılarda solunum ve bağırsak bozukluklarına neden olan tek sarmallı RNA virüsleri ailesidir. Bu ailenin altı alt tipi insanları enfekte edebilir. Bunların dördü (HCoV-NL63, HCoV-229E, HCoV-OC43 ve HKU1), bağışıklık sistemi baskılanmış kişilerde veya şiddetli solunum hastalığı olan çocuklarda ve yaşlı bireylerde hafif solunum yolu hastalığına neden olur. Diğer iki koronavirüs olan Orta Doğu Solunum Sendromu Koronavirüsü (MERS-CoV) ve Şiddetli Akut Solunum Yolu Sendromu Koronavirüsü-1 (SARSCoV-1), daha ciddi solunum yolu hastalıklarına neden olur. Son 20 yılda dünyada MERS-CoV ve SARS-CoV-1 salgınları meydana geldi ve bu virüsler yaklaşık 2.000 kişinin ölümüne sebep oldu.

Yeni bir koronavirüs üyesi olan SARS-CoV-2, ilk olarak Kasım 2019'da, Çin'in Hubei eyaletindeki Wuhan kentinde ortaya çıktı. Dünya Sağlık Örgütü ilk vakaların bildirilmesinden 3 ay sonra

11 Mart 2020'de bir pandemi durumu ilan etti. Yeni tip koronavirüs (SARS-CoV-2) enfeksiyonunun neden olduğu bir hastalık olan Koronavirüs Hastalığı-2019 (Covid-19), bir yıl içinde dünya çapında yaklaşık 130 milyon kişiyi enfekte etti ve 3 milyona yakın kişinin hayatını kaybetmesine sebep oldu. Türkiye'deki duruma baktığımızda ise, 1 yılda vaka sayılarının 3 milyona yakın olduğunu ve 30 bin civarında kişinin de hayatını kaybettiğini görmekteyiz<sup>1</sup>.

Covid-19 hastalığında insandan insana bulaşma, esas olarak doğrudan temasla veya enfekte bir kişinin öksürüğü veya hapşırmasıyla yayılan damlacıklar yoluyla gerçekleşir. SARS-CoV-2, SARS-CoV-1'den 10 kat daha büyük bir afinite ile anjiyotensin dönüştürücü enzim 2 reseptörüne (ACE2) ve transmembran serin proteaz 2'ye (TMPRSS2) bağlanır ve konakçı hücreleri istila eder<sup>2</sup>. Akciğer en çok etkilenen organlardan biridir ve tip 2 alveolar hücreler ana hedeftir. Yoğun bakım ünitesi ve ventilasyon desteği gerektiren bilateral

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- Obezite ve disfonksiyonel yağ dokusu, Covid-19 sırasında hastalığın seyrini kötüleştiren ve hastaların genel sağlığını etkileyebilen tip 2 diyabet, hipertansiyon, kardiyovasküler ve renal hastalıklar gibi komorbiditelerle ilişkilidir.

Sonuç olarak obezite, Covid-19 salgınının neden olduğu bu benzeri görülmemiş sağlık krizi bağlamında, özellikle yüksek obezite prevalansından etkilenen ülkelerde halk sağlığı stratejisinde dikkate alınması gereken bir faktördür.

## KAYNAKÇA

1. T.C. Sağlık Bakanlığı, 2021. covid19.saglik.gov.tr
2. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, 2020, 181(2):271–80. DOI:10.1016/j.cell.2020.02.052.
3. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. *The Lancet*, 2020, 395(10229):1054–62. DOI:10.1016/S0140-6736(20)30566-3.
4. Zhou P, Yang XL, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 2020, 579 (7798):270–273. DOI:10.1038/s41586-020-2012-7
5. Chen G, Wu D, Y. Cao, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. *Journal of Clinical Investigation*. 2020. DOI:10.1172/JCI137244.
6. Guan W, Liang W, Zhao Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur Respir J*. 2020, 55(5):2000547. DOI:10.1183/13993003.00547-2020.
7. Sorbello M, El-Boghdady K, Di Giacinto I, et al. The Italian coronavirus disease 2019 outbreak: recommendations from clinical practice. *Anaesthesia*. 2020, 75(6):724-732. DOI: 10.1111/anae.15049
8. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020, 395:507-513. DOI:10.1016/S0140-6736(20)30211-7
9. Adhikari SP, Meng S, Wu Y, et al. Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review. *Infect Dis Poverty*. 2020, 9(1):29. DOI:10.1186/s40249-020-00646-x
10. Grasselli G, Zangrillo A, Zanella A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*, 2020;323(16):1574-1581. DOI:10.1001/jama.2020.5394
11. Louie JK, Acosta M, Samuel MC, et al. California Pandemic (H1N1) Working Group. A novel risk factor for a novel virus: obesity and 2009 pandemic influenza A (H1N1). *Clin Infect Dis* 2011;52:301–312. DOI: 10.1093/cid/ciq152
12. Sattar N, McInnes IB, McMurray JJV. Obesity a risk factor for severe COVID-19 infection: multiple potential mechanisms. *Circulation*. 2020, 142(1):4–6. DOI: 10.1161/circulationaha.120.047659.
13. Cai Q, Chen F, Wang T, et al. Obesity and COVID-19 Severity in a Designated Hospital in Shenzhen, China, *Diabetes Care* 2020, 43:1392–1398. DOI: 10.2337/dc20-0576
14. Nakeshbandi M, Maini R, Daniel P, et al. The impact of obesity on COVID-19 complications: a retrospective cohort study, *International Journal of Obesity*, 2020, 44:1832–1837. DOI: 10.1038/s41366-020-0648-x
15. Gao F, Zheng KI, Wang XB, et al. Obesity Is a Risk Factor for Greater COVID-19 Severity Diabetes Care 2020;43:e72–e74. | DOI: 10.2337/dc20-0682
16. Simonnet A, Chetboun M, Poissy J, et al. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. *Obesity*. 2020 DOI: 10.1002/oby.22831.
17. Caussy C, Wallet F, Laville M, et al. Obesity is Associated with Severe Forms of COVID-19, *Obesity*, 2020, 28(7), 1175. DOI: 10.1002/oby.22842.
18. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospitalization and critical illness among 4,103 patients with COVID-19 disease in New York City. *medRxiv*, 2020. DOI: 10.1101/2020.04.08.20057794 (2020).
19. Lighter J, Phillips M, Hochman S, et al. Obesity in patients younger than 60 years is a risk factor for COVID-19 hospital admission. *Clin Infect Dis*. 2020. doi:10.1093/cid/ciaa415.
20. Klang E, Kassim G, Soffer S, et al. Severe Obesity as an Independent Risk Factor for COVID-19 Mortality in Hospitalized Patients Younger than 50, *Obesity*, 2020, 28(9), 1595-1599. DOI: 10.1002/oby.22913
21. Busetto L, Bettini S, Fabris R, et al. Obesity and COVID 19: An Italian Snapshot, *Obesity*, 2020, 28(9),1600-1605. DOI: 10.1002/oby.22918
22. Moser JS, Galindo-Fraga A, Ortiz-Hernández AA, et al. Underweight, overweight, and obesity as independent risk factors for hospitalization in adults and children from influenza and other respiratory

- viruses. *Influenza Other Respi Viruses*. 2019, 13(1), 3-9. DOI: 10.1111/irv.12618
23. Maccioni L, Weber S, Elgizouli M, et al. Obesity and risk of respiratory tract infections: results of an infection-diary based cohort study. *BMC Public Health*. 2018, 18(1), 271. DOI: 10.1186/s12889-018-5172-8
  24. Smith AG, Sheridan PA, Harp JB, et al. Diet-induced obese mice have increased mortality and altered immune responses when infected with influenza virus. *J Nutr*. 2007, 137:1236-1243. DOI: 10.1093/jn/137.5.1236
  25. Rello J, Rodríguez A, Ibañez P, et al. Intensive care adult patients with severe respiratory failure caused by influenza A (H1N1)v in Spain. *Crit Care*. 2009, 13(5):R148.
  26. Duarte AG, Justino E, Bigler T, Grady J. Outcomes of morbidly obese patients requiring mechanical ventilation for acute respiratory failure. *Crit Care Med*, 2007, 35:732-737. DOI: 10.1097/01.CCM.0000256842.39767.41
  27. Peppard PE, Young T, Barnet JH, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000, 284:3015-3021. DOI: 10.1001/jama.284.23.3015
  28. Peters U, Dixon AE. The effect of obesity on lung function. *Expert Rev Respir Med*. 2018, 12(9):755-767. DOI: 10.1080/17476348.2018.1506331
  29. Franceschi C, Bonaf M, Valensin S, et al. Inflamm-aging: An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences*, 2000, 908:244-54. DOI: 10.1111/j.1749-6632.2000.tb06651.x.
  30. Houston DK, Nicklas BJ, Zizza CA. Weighty concerns: The growing prevalence of obesity among older adults. *Journal of the American Dietetic Association*, 2009, 109 (11):1886-95. DOI: 10.1016/j.jada.2009.08.014.
  31. Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *Int J Oral Sci*. 2020, 12(1):8. DOI: 10.1038/s41368-020-0074-x.
  32. Monteil VKH, Prado P, Hagelkrüys A, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell*. 2020, 181(4):905-913. DOI: 10.1016/j.cell.2020.04.004. Accessed April 24, 2020.
  33. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020, 383:120-128. DOI: 10.1056/bloNEJMoa2015432.
  34. Yao L, Bhatta A, Xu Z, et al. Obesity-induced vascular inflammation involves elevated arginase activity. *Am. J. Physiol. Regul. Integr. Comp. Physiol*. 2017, 313, R560-R571. DOI: 10.1152/ajpregu.00529.2016
  35. Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. *Curr Opin Hematol*. 2013, 20(5), 437-444. DOI: 10.1097/MOH.0b013e3283634443.
  36. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020, 18(4):844-847. DOI: 10.1111/jth.14768.
  37. Marietta M, Coluccio V, Luppi M. COVID-19, coagulopathy and venous thromboembolism: more questions than answers. *Intern Emerg Med*. 2020;1-13. DOI: 10.1007/s11739-020-02432-x.
  38. Bladbjerg EM, Stolberg CR, Juhl CB. Effects of obesity surgery on blood coagulation and fibrinolysis: a literature review. *Thromb Haemost* 2020;120:579-591.
  39. Vaduganathan M, Vardeny O, Michel T, et al. Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. *N Engl J Med*. 2020;382:1653-1659. DOI: 10.1056/NEJMsr2005760
  40. de Pinheiro TA, Barcala-Jorge AS, Andrade JMO, et al. Obesity and malnutrition similarly alter the renin-angiotensin system and inflammation in mice and human adipose. *J Nutr Biochem*. 2017, 48, 74-82. DOI: 10.1016/j.jnutbio.2017.06.008
  41. Ruan Q, Yang K, Wang W, et al. Clinical predictors of mortality due to COVID-19 based on an analyses of data of 150 patient from Wuhan. *China Intensive Care Med*. 2020;46(5):846-848. DOI: 10.1007/s00134-020-05991-x
  42. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan. *The Lancet*, 2020, 395 (10223):497-506. DOI: 10.1016/S0140-6736(20)30183-5.
  43. Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol*. 2020, 146(1), 128-136. DOI: 10.1016/j.jaci.2020.05.008.
  44. Misumi I, Starmer J, Uchimura T, et al. Obesity expands a distinct population of T cells in adipose tissue and increases vulnerability to infection. *Cell Rep*. 2019; 27(2):514-524. DOI: 10.1016/j.cellrep.2019.03.030
  45. Cardone M, Yano M, Rosenberg AS, Puig M. Lessons learned to date on COVID-19 hyperinflammatory syndrome: considerations for interventions to mitigate SARS-CoV-2 viral infection and detrimental hyperinflammation. *Front Immunol*. 2020, 11, 1131. DOI: 10.3389/fimmu.2020.01131
  46. Francisco V, Pino J, Campos-Cabaleiro V, et al. Obesity, fat mass and immune system: Role for leptin. *Frontiers in Physiology*, 2018, 9:640. DOI: 10.3389/fphys.2018.00640.

47. Heinonen S, Saarinen L, Naukkarinen J, et al. Adipocyte morphology and implications for metabolic derangements in acquired obesity. *Int J Obes*, 2014, 38(11), 1423-1431. DOI: 10.1038/ijo.2014.31
48. de Oliveira LV, Mafra D. Adipokines in obesity. *Clin Chim Acta*. 2013, 419, 87-94. DOI: 10.1016/j.cca.2013.02.003
49. Stapleton RD, Dixon AE, Parsons PE, et al. Acute Respiratory Distress Syndrome Network. The association between BMI and plasma cytokine levels in patients with acute lung injury. *Chest*. 2010, 138(3), 568-577. DOI: 10.1378/chest.10-0014
50. Matarese G, Procaccini C, De Rosa V, et al. Regulatory T cells in obesity: The leptin connection. *Trends in Molecular Medicine*, 2010, 16 (6):247-56. DOI: 10.1016/j.molmed.2010.04.002.
51. Caldefie-Chezet F, Pouli A, Vasson MP. Leptin regulates functional capacities of polymorphonuclear neutrophils. *Free Radical Research*, 2013, 37(8):, 09-14. doi: 10.1080/1071576031000097526.
52. Montecucco F, Bianchi G, Gnerre P, et al. Induction of neutrophil chemotaxis by leptin: Crucial role for p38 and Src kinases. *Annals of the New York Academy of Sciences*, 2006, 1069, 463-71. doi: 10.1196/annals.1351.045.
53. Zarkesh-Esfahani H, Pockley AG, Wu Z, et al. Leptin indirectly activates human neutrophils via induction of TNF-alpha. *Journal of Immunology*, 2004, 172(3), 1809-1814. doi: 10.4049/jimmunol.172.3.1809.
54. Ubags ND, Vernooy JH, Burg E, et al. The role of leptin in the development of pulmonary neutrophilia in infection and acute lung injury. *Critical Care Medicine*, 2014, 42(2), 143-151. DOI: 10.1097/CCM.0000000000000048.
55. Ohashi K, Parker JL, Ouchi N, et al. Adiponectin promotes macrophage polarization toward an anti-inflammatory phenotype. *J Biol Chem*. 2010, 285(9), 6153-6160. DOI: 10.1074/jbc.M109.088708
56. Walkey AJ, Rice TW, Konter J, et al. Plasma adiponectin and mortality in critically ill subjects with acute respiratory failure. *Crit Care Med*. 2010, 38(12), 2329-2334. DOI: 10.1097/CCM.0b013e-3181fa0561
57. Summer R, Little FF, Ouchi N, et al. Alveolar macrophage activation and an emphysema-like phenotype in adiponectin-deficient mice. *Am J Physiol Lung Cell Mol Physiol*. 2008, 294(6),1035-1042. DOI: 10.1152/ajplung.00397.2007
58. Ahl S, Guenther M, Zhao S, et al. Adiponectin levels differentiate metabolically healthy vs unhealthy among obese and nonobese white individuals. *J Clin Endocrinol Metab*. 2015, 100(11), 4172-4180. DOI: 10.1210/jc.2015-2765.
59. Roth J, Qiang X, Marban SL, et al. The obesity pandemic: Where have we been and where are we going? *Obesity Research*, 2004, 12(S11):88S-101S. DOI: 10.1038/oby.2004.273.
60. Ryan PM, Caplice NM. Is adipose tissue a reservoir for viral spread, immune activation, and cytokine amplification in coronavirus disease 2019? *Obesity*, 2020, 28(7), 1191-1194. DOI: 10.1002/oby.22843
61. Torrealba MP, Manfrere KC, Miyashiro DR, et al. Chronic activation profile of circulating CD8 $\beta$  T cells in S<sub>ezary</sub> syndrome. *Oncotarget*, 2018, 9(3):3497-3506. DOI: 10.18632/oncotarget.23334.
62. Chiappelli F, Khakshooy A, Greenberg G. CoViD-19 immunopathology and immunotherapy. *Bioinformatics*, 2020, 16(3):219-22. DOI: 10.6026/97320630016219.
63. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. *The Journal of Clinical Endocrinology and Metabolism*, 2004, 89 (6):2548-56. DOI: 10.1210/jc.2004-0395.
64. Tsao YC, Chen JY, Yeh WC, Li WC. Gender and age specific associations between visceral obesity and renal function impairment. *Obes Facts*. 2019, 12:67-77. DOI: 10.1159/000496626.
65. Calder PC, Carr AC, Gombart AF, Eggersdorfer M. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. *Nutrients*. 2020, 12(4), 1181. DOI: 10.3390/nu12041181.
66. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020, 12(4), 988. DOI: 10.3390/nu12040988.
67. Belderbos ME, Houben ML, Wilbrink B, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. *Pediatrics*, 2011, 127 (6), 1513-20. DOI: 10.542/peds.2010-3054.
68. Khare D, Godbole NM, Pawar SD, et al. Calcitriol [1, 25(OH)<sub>2</sub> D<sub>3</sub>] pre- and post-treatment suppresses inflammatory response to influenza A (H1N1) infection in human lung A549 epithelial cells. *European Journal of Nutrition*, 2013, 52 (4):1405-15. DOI: 10.1007/s00394-012-0449-7.
69. Wang TT, Nestel FP, Bourdeau V, et al. Cutting edge: 1,25-dihydroxyvitamin D<sub>3</sub> is a direct inducer of antimicrobial peptide gene expression. *Journal of Immunology*, 2004, 173 (5):2909-2912. doi: 10.4049/jimmunol.173.5.2909.
70. Pourshahidi LK, Vitamin D and obesity: Current perspectives and future directions. *Proceedings of the Nutrition Society*, 2015, 74 (2):115-24. DOI: 10.1017/S0029665114001578.



71. Botella-Carretero JI, Balsa JA, Vazquez C, et al. Retinol and alpha-tocopherol in morbid obesity and nonalcoholic fatty liver disease. *Obesity Surgery*, 2010, 20(1):69–76. DOI:10.1007/s11695-008-9686-5.
72. Cui W, Zhang P, Gu J, et al. Vitamin A deficiency promotes inflammation by induction of type 2 cytokines in experimental ovalbumin-induced asthma murine model. *Inflammation*, 2016, 39(5):1798–1804. DOI: 10.1007/s10753-016-0415-2.
73. Wu, J., Y. Zhang, Q. Liu, W. Zhong, and Z. Xia. 2013. All-trans retinoic acid attenuates airway inflammation by inhibiting Th2 and Th17 response in experimental allergic asthma. *BMC Immunology* 14:28. doi: 10.1186/1471-2172-14-28.
74. Cepeda-Lopez AC, Osendarp SJ, Melse-Boonstra A, et al. Sharply higher rates of iron deficiency in obese Mexican women and children are predicted by obesity-related inflammation rather than by differences in dietary iron intake. *The American Journal of Clinical Nutrition*, 2011, 93 (5):975–83. DOI: 10.3945/ajcn.110.005439.
75. Bonaccorsi-Riani E, Danger R, Lozano JJ, et al. Iron deficiency impairs intra-hepatic lymphocyte mediated immune response. *PLoS One*, 2015, 10 (8): e0136106. DOI: 10.1371/journal.pone.0136106.
76. Gonzalez-Muniesa P, Martinez-Gonzalez MA, Hu FB, et al. Obesity. *Nat. Rev. Dis. Prim.* 2017, 3, 17034.
77. Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health*, 2009, 9, 88. DOI:10.1186/1471-2458-9-88
78. Tobias DK, Hu FB, The association between BMI and mortality: implications for obesity prevention. *Lancet Diabetes Endocrinol.* 2018, 6, 916–917. DOI: 10.1016/S2213-8587(18)30309-7
79. Carrillo-Vega MF, Salinas-Escudero G, Garcia-Peña C, et al. Early estimation of the risk factors for hospitalisation and mortality by COVID-19 in Mexico. *PLoS ONE*, 15(9): e0238905. DOI: 10.1371/journal.pone.0238905
80. Erener S. Diabetes, infection risk and Covid-19. *Mol. Metab.* 2020, 39, 101044. DOI: 10.1016/j.molmet.2020.101044
81. Louwen F, Ritter A, Kreis NN, Yuan J. Insight into the development of obesity: Functional alterations of adipose-derived mesenchymal stem cells. *Obes. Rev.* 2018, 19, 888–904. DOI: 10.1111/obr.12679
82. Tsalamandris S, Antonopoulos AS, Oikonomou E, et al. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. *Eur. Cardiol.* 2019, 14(1), 50–59. DOI: 10.15420/ecr.2018.33.1
83. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2018, 103(5), 1715-1744. DOI: 10.1210/jc.2018-00229
84. Mohamad NV, Wong SK, Hasan WNW, et al. The relationship between circulating testosterone and inflammatory cytokines in men. *Aging Male.* 2019, 22(2), 129-140. DOI: 10.1080/13685538.2018.1482487.
85. Jackson SE, Kirschbaum C, Steptoe A. Hair cortisol and adiposity in a population-based sample of 2,527 men and women aged 54 to 87 years. *Obesity.* 2017, 25(3), 539-544. DOI: 10.1002/oby.21733.
86. Pal R. COVID-19, hypothalamo-pituitary-adrenal axis and clinical implications. *Endocrine.* 2020, 68(2), 251-252. DOI: 10.1007/s12020-020-02325-1.
87. Wheatland R. Molecular mimicry of ACTH in SARS – implications for corticosteroid treatment and prophylaxis. *Med Hypotheses.* 2004; 63(5):855-862. DOI: 10.1016/j.mehy.2004.04.009.
88. The RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with Covid-19 – preliminary report. *N Eng J Med.* 2020 Jul 17;NEJMoa2021436. DOI: 10.1056/NEJMoa2021436.